REMARKS

Status of the claims

With entry of the instant amendment, claim 1 has been amended and new claim 24 has been added. Claims 1-8, 10-13, and 22-24 are therefore pending and under examination.

Claim1 has been amended to reflect that the the lyophilized mixture forms a clear solution when dissolved in water. This amendment adds no new matter. Support for the amendment can be found, *e.g.,* at paragraph 28.

New claim 24 reflects that the lyophilized mixture forms a clear solution when dissolved in an amount of water that provides a concentration of 1 mM thrombin substrate and 15 mM $CaCl_2$. Support can be found, *e.g.,* at paragraph 50.

Rejection under 35 U.S.C. § 103

The Examiner has maintained the rejection of claims 1-8, 10-13, 22 and 23 as allegedly obvious over U.S. Patent No. 6,124,110 to Wöber *et al.*; U.S. Patent No. 5,625,036 to Hawkins *et al.*; Lawson *et al.*, *J. Biol. Chem.* 267(7): 4834-4843 (1992); Váradi *et al.*, *J. Thromb. Haemostasis* 1:2374-2380 (2003); U.S. Patent No. 5,952,198 to Chan; U.S. Patent No. 6,074,826 to Hogan *et al.*; U.S. Patent No. 6,576,422 to Weinstein *et al.*; U.S. Patent No. 6,756,019 to Dubrow *et al.*, U.S. Patent Publication No. 2002/0151582 to Dou *et al*; and p. B-77 of the CRC Handbook of Chemistry and Physics 51st ed., R.C. Weast, ed. Applicants traverse this rejection for reasons of record and for the reasons additionally set forth below.

In response to the Declaration under 37 C.F.R. § 1.132 by Peter Turecek filed April 16, 2008 ("the Turecek II Declaration"), the Examiner contends that the data presented therein are insufficient to overcome the obviousness rejection. Several reasons are set forth in the Office Action dated May 1, 2008. In particular, the Examiner alleges that in the experiments presented in the Turecek II Declaration, there were differences in the formation of precipitates in microtiter plate wells vs. glass vials, that the concentrations employed were higher than those employed by Váradi *et al.* and that no data comparing the solubility of individually lyophilized fluorescent thrombin substrate to the solubility of a lyophilized thrombin substrate/$CaCl_2$ mixture

were presented. The Examiner maintains that in view of these omissions, the Turecek II Declaration does not properly support the nonobviousness of the claims. Although Applicants do not necessarily agree with the Examiner's position, in the interests of expediting prosecution, Applicants provided herewith a further Declaration under 37 C.F.R. § 1.132 by Peter Turecek ("the Turecek III Declaration") to further address the specific issues raised by the Examiner.

First, it is noted that the experimental data provided in the Turecek III Declaration evaluates the solubility using glass vials only so that each of the sample types and re-solubilization procedures is performed in the same type of container. Applicants further note that Example 4, paragraph 48 of the specification provides further evidence that a lyophilized mixture comprising the fluorescent thrombin substrate and $CaCl_2$ that is lyophilized in a microtiter plate (as opposed to a glass vial) is also soluble in an aqueous solution to which DMSO has not been added. The data in Example 4 show thrombin generation where the lyophilized TF/PL-complex and the lyophilized thrombin substrate/$CaCl_2$ mixture are present together in one well of a microtiter plate in comparison to where the lyophilized TF/PL-complex is lyophilized separately from the lyophilized thrombin substrate/$CaCl_2$ mixture. Regardless of whether the thrombin substrate/$CaCl_2$ is lyophilized with the TF/PL-complex or separately from the TF/PL complex, it is soluble in an aqueous solution, *e.g.*, plasma, without DMSO (see, Figure 4).

Please note that the photographs in Exhibit 2 of the Turecek III Declaration are filed in color. The solubility of the substrates shown in the photographs in Exhibit 2, however, may be difficult to see in the black and white version of the photographs that is scanned into the electronic file wrapper. Applicants are happy to arrange to provide additional color copies of Exhibit 2 if the Examiner believes that it will be helpful.

The Turecek III Declaration evaluates four types of lyophilized samples that contain the fluorescent thrombin substrate. These samples are as follows.

Sample 1: The concentration of substrate in sample 1 (prior to lyophilization) was 5 mM with 10% DMSO--no $CaCl_2$ is present in the lyophilized sample;

Sample 2: The concentration of substrate in sample 2 (prior to lyohpilization) was 2.5 mM, 5% DMSO--no $CaCl_2$ is present in the lyophilized sample;

Sample 3: The concentration of substrate in sample 3 (prior to lyophilization) was 1 mM. The lyophilized sample also contained 15 mM $CaCl_2$ and 2% DMSO; and

Sample 4: The concentration of substrate, $CaCl_2$, and DMSO is the same as Sample 3; the concentration of the buffer components are different.

The results show that when the $CaCl_2$ and substrate are lyophilized together as a mixture, the mixture is readily soluble in water or buffer (reconstitution experiments 3 and 4), whereas when the thrombin substrate is lyophilized separately and then re-solubilized with water or buffer under the conditions set forth in experiments 1 and 2, or using a 15 mM calcium chloride solution (experiment 1a), it is very difficult to dissolve. For example, when the substrate in sample 1 vials is dissolved in 5 mls of 15 mM $CaCl_2$ to provide a substrate concentration of 1 mM (experiment 1a), the lyophilized substrate is barely soluble.

Dr. Turecek explains that the ready solubility of the lyophilized fluorescent substrate/$CaCl_2$ mixture was a surprising finding. The obviousness rejection set forth in the office action provides no reasoning or evidence that one of skill would have been able to predict that the lyophilized mixture would be readily soluble in an aqueous solution, *e.g.*, water.

Any differences between the claimed invention and the prior art may be expected to result in some difference in properties. The issue is whether the properties differ to such an extent that the difference is really unexpected (MPEP § 716.02) Here, fluorescent thrombin substrates are known to have only limited solubility in water (*e.g.*, the Turecek II Declaration). One of skill would logically have expected that this would hold true when the substrate is lyophilized together as a mixture with the $CaCl_2$. The inventors discovered that this was not the case. This unexpected result is sufficient to establish unobviousness (absence of an expected property is evidence of nonobviousness, MPEP § 715.02(a)(IV).

In view of the foregoing, the claims are patentable over the cited art. Applicants therefore respectfully request withdrawal of the rejection.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,

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